Complete Summary

GUIDELINE TITLE

Prevention of venous thrombosis.

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Prevention of venous thrombosis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008 Mar 27 [Various]. [5 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Prevention of venous thrombosis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2006 May 3 [Various].

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Venous thrombosis

GUIDELINE CATEGORY

Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Hematology
Internal Medicine
Neurology
Obstetrics and Gynecology
Oncology
Orthopedic Surgery
Surgery

INTENDED USERS

Health Care Providers
Physicians

GUIDELINE OBJECTIVE(S)

Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.

TARGET POPULATION

Patients at risk for venous thrombosis

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention

1. Classification of surgical patients into low-, moderate-, and high-risk groups

2. Preventive measures in surgical patients
    - Nonpharmacologic measures such as early mobilization and compression stockings
    - Pharmacologic prophylaxis
        - Warfarin
        - Low-molecular weight heparins: enoxaparin, dalteparin
        - Fondaparinux

3. Risk assessment and prophylaxis in internal medicine and neurologic disease patients
4. Risk assessment and prophylaxis during pregnancy including special care units
5. Evaluation and management of heparin-induced thrombocytopenia and thrombosis

MAJOR OUTCOMES CONSIDERED

- Efficacy of prophylactic measures at reducing the risk and rates of deep venous thrombosis and/or pulmonary embolism
- Side effects of therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The evidence reviewed was collected from the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). In addition, the Cochrane Library and medical journals were searched specifically for original publications.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of the Quality of Evidence

Code	Quality of Evidence	Definition
A	**High**	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial
B	**Moderate**	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	**Low**	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	**Very Low**	Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations

GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the EBM Guidelines Editorial Team).

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence [A-D] supporting the recommendations are defined at the end of the "Major Recommendations" field.

See the National Guideline Clearinghouse (NGC) summary of the American College of Chest Physicians guideline Prevention of Venous Thrombosis.

Basic Rules

- Venous thrombosis is a common and dangerous disease that can, however, be treated and often prevented.
- Venous thrombosis of a bedridden patient can be asymptomatic--the first symptom may be pulmonary embolism.
- Early mobilisation, antiembolism stockings, low molecular weight heparin (LMWH), and warfarin are used for primary prevention. Aspirin (ASA) is primarily used for the prevention of arterial occlusion.
- Aspirin may also reduce the incidence of venous thrombosis ("Collaborative overview," 1994) [**A**] However, as evidence of benefit is lacking (Philbrick et al., 2007) [**D**], aspirin is no longer recommended as prophylaxis (e.g., on long haul flights) (Geerts et al., 2004)
    - On long flights it is recommended that high risk patients wear antiembolism stockings (Clark et al., 2006) [**A**].
    - LMWH may also be used if the patient has known thrombophilia or a history of thromboembolism and is not on warfarin (one dose of prophylaxis half an hour prior to flight).
- If the patient is under 40 years of age and has a venous thrombosis without any causative factors, consider the possibility of a hereditary coagulation disorder.
- In addition to hereditary (intrinsic) factors there are extrinsic factors and conditions that contribute to venous thrombosis:
    - Previous venous thrombosis
    - Oral contraceptives
    - Pregnancy, labour, and puerperium 6 weeks
    - Surgery and tissue trauma
    - Varicose veins

- Obesity
- Polycythaemia, essential thrombocytosis, dehydration
- Heart insufficiency and immobilisation
- Paralysis, inactivity
- Malignant diseases
- Immobilization (cast, long flights)

Prevention of Venous Thrombosis in Surgery

- Low risk (risk of venous thrombosis 2% to 3% [-10%])
  - Minor surgery (<30 min), no risk factors
  - Age <40, no risk factors
- Moderate risk (risk of venous thrombosis 10% to 30%)
  - Minor surgery, risk factors
  - Nonmajor surgery, no risk factors, age 40 to 60
  - Major surgery, age under 40, no risk factors
- High risk (risk of venous thrombosis 50% to 80%)
  - Major surgery, age >40 years, and earlier deep venous thrombosis or pulmonary embolism or cancer
  - Thrombophilia
  - Knee or hip arthroplasty, hip fracture
  - Major trauma, injury of the spinal cord
- The estimated risk of venous thrombosis in the above-mentioned risk groups is about 10%, 30%, and 60%, respectively. In classifying patients into risk groups, take into account both the personal predisposing factors and the type of surgery. Give prophylactic medication against thrombosis to patients belonging to the moderate or high-risk groups. Low-molecular-weight heparin (LMWH) is safe and easily administered at home. It should be used more often for the low-risk patients and the course of medication should be prolonged in high-risk patients.
- Immobilization increases the risk of thrombosis (e.g., an ankle fracture in a cast involves a 20% risk, and a fractured tibia in a cast a 60% risk).

How to Prevent Thrombosis in Surgical Patients

- Avoid immobilization before and after surgery, avoid general anaesthetics and prefer spinal or epidural anaesthetics, optimize the fluid balance.
- Start preventive therapy before the operation, if possible (Hull et al., 1999) [**C**].
- Among the available physical measures the most common and easiest are compression dressings or a surgical stocking (Amaragiri & Lees, 2000; Wells, Lensing, & Hirsh, 1994; Agu, Hamilton, & Baker, 1999) [**A**], which in low-risk patients suffice as the only methods of prevention. Their usefulness has been shown in surgical and obstetric patients.
- Early mobilization does not mean that the patient is placed in a sitting position: mere sitting may even increase the risk of thrombosis.
- Warfarin can also be used for prophylaxis, as it is practical and inexpensive, and can be used when long-term prophylaxis is needed (e.g., a fractured pelvis and long immobilization). The use of warfarin involves the risk of bleeding and requires regular monitoring.
- Heparin is effective in reducing the incidence of deep vein thrombosis (Handoll et al., 2002; Palmer et al., 1997; Howard & Aaron, 1998) [**A**].

LMWHs have displaced ordinary heparin because of their higher efficacy and easy administration (once daily). If the immobilization is prolonged, continue heparin treatment until the patient is able to get up again. Prophylactic treatment with LMWH is safe and often possible to carry out at home. Treatment duration is 4 weeks in hip (Hull et al., 2001) [**A**] and knee prosthesis surgery and in cancer surgery (Bergqvist et al., 2002) [**B**], 6 weeks during pregnancy and puerperium. In a high-risk group the treatment can be continued with warfarin for 6 to 12 weeks. A nurse making home visits may help in the administration of LMWH.

- The usual prophylactic treatment scheme with LMWH
    - Moderate risk patients
        - Enoxaparin 20 (–40) mg subcutaneous (s.c) 2 hours before surgery and then the same amount once daily
        - Dalteparin 2500 IU 2 hours before surgery and then the same amount once daily
    - High risk patients
        - Fondaparinux 2.5 mg s.c. once daily, started 6 hours after surgery. Fondaparinux is an inhibitor of coagulation factor X, that prevents venous thrombosis in association with orthopaedic surgery more efficiently than enoxaparin (Turpie et al., 2004; Agnelli et al., 2005; Garces & Mamdani, 2002; "Fondaparinux," 2001) [**A**].
        - Enoxaparin 40 mg s.c. 12 hours before surgery and then the same amount once daily
        - Dalteparin 5000 IU 12 hours before surgery and then the same amount once daily
- Adverse effects: postoperative and post-traumatic bleeding. The antidote is protamine.

Prevention of Venous Thrombosis in Internal Medicine and in Neurological Diseases

Risk Factors for Venous Thrombosis

- Heart failure and other non-surgical high-risk patients
- Heart failure and myocardial infarction
- Pulmonary embolism is a common cause of death of patients with infarction of the brain. The risk can be lowered with early mobilisation, antiembolism stockings, and LMWH. Haemorrhage complications diminish the benefits.
- Cancer
- Severe infection

Implementation

- LMWH therapy should be considered for all patients who are at bed rest for more than 3 days and who have one or more of the above-mentioned risk factors. The treatment is often continued with warfarin if the need for prophylaxis is prolonged.

Prevention of Venous Thrombosis in Neoplastic Diseases

- Active, and especially metastatic, cancer elevates the risk of venous thrombosis. Thromboembolism that appears without apparent reason may be the first sign of a latent malignant disease.
- Even if thrombosis prophylaxis in indicated, it is still underused: the reason for this is that the disease itself and its treatment usually raise the risk of haemorrhaging. Prophylaxis is started on an individual basis after careful consideration of indications and contraindications.
- Warfarin often interacts with treatments used in cancer patients and for this reason LMWH is considered a safer and more effective alternative for these patients.
- The greatest risk is associated with lower abdominal cancer surgery. Prophylaxis is carried out by administering LMWH for one month: enoxaparin 40 mg × 1 or dalteparin 5000 IU × 1.
- The risk is also elevated in patients who have a history of venous thrombosis during earlier immobilization or infection, or who have additional risk factors for venous thrombosis. Prophylaxis is usually indicated at least during bedrest.

Prevention of Venous Thrombosis During Pregnancy

- Carried out in special care units

High Risk of Thromboembolism

- A venous thrombus above the knee, or pulmonary embolism during an earlier pregnancy.
- Patients with a hereditary or acquired blood coagulation disorder and a previous venous thrombosis. (In antithrombin III deficiency the risk is so high that prophylactic treatment must always be given, even if the patient has no history of thrombosis).
    - Acquired coagulation disorders include (e.g., lupus anticoagulant and myeloproliferative diseases [e.g., polycythaemia vera, essential thrombocytosis]).

Treatment in Special Care Units

- Start prophylactic treatment with LMWH after confirming the pregnancy, or at the latest on weeks 16-18. Mini-heparin treatment is not sufficient! Continue antithrombotic therapy for 6 weeks after parturition; however, at the time of delivery the drug can be changed to oral warfarin, which is contraindicated during pregnancy. The risk of thrombosis is highest at the end of the pregnancy, and higher doses of LMWH are often used.
- The initiation of heparin treatment depends on the risk: in women who have had thromboembolism during an earlier pregnancy or on oral contraceptives the treatment should always be started on week 24 at the latest.
- Prophylactic treatment in patients with activated protein C (APC) resistance due to genetic defect of factor V (see the Finnish Medical Society Duodecim guideline on "Inherited Thrombophilia"):
    - Heterozygotes who have not had a thrombosis: prophylactic treatment is recommended only in cases of caesarean section or immobilization.
    - Heterozygotes who have had a thrombosis: prophylactic treatment is recommended during pregnancy and puerperium.

- Homozygotes: prophylactic treatment is recommended regardless of whether the patient has had a thrombosis or not.

Thrombocytopenia and Thrombosis as Complications of Heparin Treatment

- Early thrombocytopenia is benign and caused by aggregation of thrombocytes.
- Severe immunologically mediated thrombocytopenia leads to activation of thrombocytes and endothelial damage, causing arterial thrombi.
- Symptoms are caused by arterial or venous thrombosis during weeks 1-3 of the treatment. The onset is typically on the fifth or the tenth day from the beginning of the treatment.
- The laboratory finding is a clear decrease in the thrombocyte count (or a value below 100 in one measurement). Thrombocytopenia occurs in approximately 1% of LMWH users (Prandoni et al., 2005)
- In the follow-up of heparin treatment, haemoglobin and thrombocyte values should be taken at 1-week intervals for 4 weeks.
    - Actions are required if the thrombocyte count falls below 50% from the baseline value, if the thrombocytopenia is progressing, or if the antithrombotic treatment proves ineffective.
    - Do not start warfarin treatment before the thrombocyte count is normalized.
- Platelet transfusions are contraindicated. Consult a haematologist.
- Alternative anticoagulants: fondaparinux, danaparoid, lepidurin

Related Resources

Refer to the original guideline document for related evidence, including Cochrane reviews and other evidence summaries.

Definitions:

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B	**Moderate**	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • One high-quality study

Code	Quality of Evidence	Definition
		• Several studies with some limitations
C	**Low**	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Concise summaries of scientific evidence attached to the individual guidelines are the unique feature of the Evidence-Based Medicine Guidelines. The evidence summaries allow the clinician to judge how well-founded the treatment recommendations are. The type of supporting evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Early detection and prevention of venous thrombosis
- Appropriate use of prophylactic measures for prevention of venous thrombosis

POTENTIAL HARMS

- An adverse effects of warfarin therapy is bleeding
- Adverse effects of heparin therapy include bleeding, and thrombocytopenia and thrombosis

CONTRAINDICATIONS

CONTRAINDICATIONS

- Oral warfarin is contraindicated during pregnancy.
- Platelet transfusions are contraindicated for treatment of heparin-induced thrombocytopenia and thrombosis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Prevention of venous thrombosis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008 Mar 27 [Various]. [5 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Mar 6 (revised 2008 Mar 27)

GUIDELINE DEVELOPER(S)

Finnish Medical Society Duodecim - Professional Association

SOURCE(S) OF FUNDING

Finnish Medical Society Duodecim

GUIDELINE COMMITTEE

Editorial Team of EBM Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Author: Markku Ellonen

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Prevention of venous thrombosis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2006 May 3 [Various].

GUIDELINE AVAILABILITY

This guideline is included in "EBM Guidelines. Evidence-Based Medicine" available from Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com; Web site: www.ebm-guidelines.com.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on August 30, 2005. This NGC summary was updated by ECRI on July 13, 2006. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory

on heparin sodium injection. This NGC summary was updated by ECRI Institute on December 2, 2008.

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